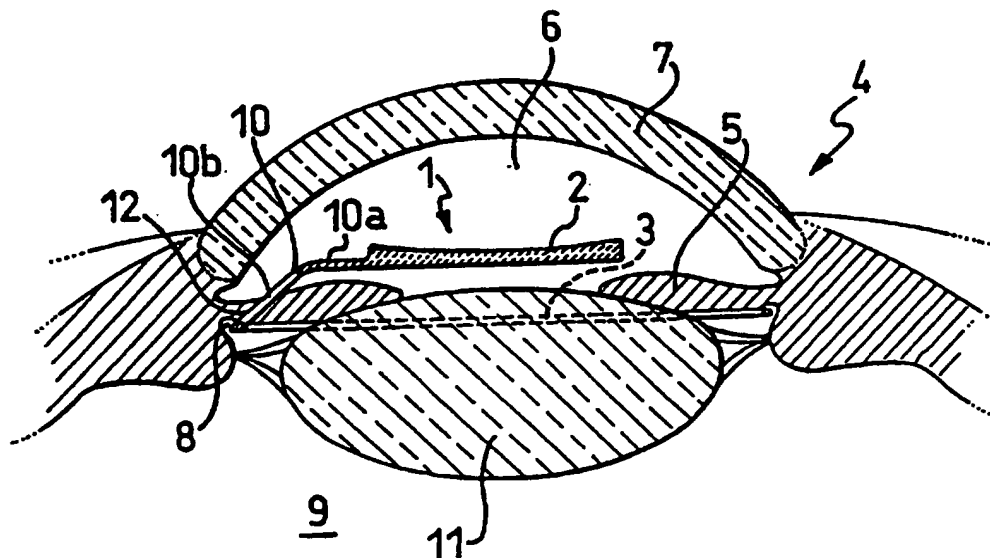




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(21) International Application Number: PCT/EP97/00408 (22) International Filing Date: 30 January 1997 (30.01.97) (30) Priority Data: M196A000181 2 February 1996 (02.02.96) IT (71) Applicant (for all designated States except US): SOLEKO S.P.A. [IT/IT]; Via Ravano, I-03037 Pontecorvo (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): PIVOVAROV, Nicolay [RU/IT]; Via le Tevere, 34/10, I-64029 Silvi Marina (IT). KAWAMUKAI, Motokage [JP/IT]; Via Cicerone Snc., I-03037 Pontecorvo (IT). (74) Agent: BOTTERO, Claudio; Porta, Checcacci & Botti S.r.l., Viale Sabotino, 19/2, I-20135 Milano (IT).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: **INTRAOCULAR LENS**

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(57) Abstract

An intraocular lens comprises a lens portion (2) connected to at least one supporting loop (3, 14, 15), substantially shaped as an arc of a circle having a diameter substantially equal to the diameter of the ciliary groove (8) of the eye (4), for fixing the lens therein. Advantageously, the supporting loop or loops (3, 14, 15) are posteriorly connected to said lens portion (2) at a distance (d) such that, once the lens is implanted, the supporting loop or loops (3, 14, 15) are positioned in the ciliary groove (8) of the eye (4) and the lens portion (2) is positioned in the anterior chamber (6) of said eye (4) with no physical contact neither with the iris (5) nor with the crystalline lens (11) nor with the cornea (7).

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Title: "Intraocular lens"

DESCRIPTION

Technical Field

5 In a general aspect, the present invention relates to an artificial intraocular lens suitable to correct visual and/or refractive defects both in phakic eyes (i.e. in the presence of the natural crystalline lens) and in aphakic eyes (without the crystalline lens).

10 The present invention relates, more particularly, to an intraocular lens of the type comprising a lens portion connected to at least one supporting loop, substantially shaped as an arc of a circle with diameter substantially equal to the diameter of the ciliary groove of the human eye, for fixing the lens therein.

15 As is known, the human eye is an extremely complex organ and comprises various mutually interacting elements for collecting, focusing and transmitting light and images to the nerve endings connected to the retina, which are in turn delegated to transmit a signal to the brain which
20 processes them to allow vision.

More particularly, the intensity of the light transmitted to the retina is regulated by the greater or smaller pupil diameter (diaphragmation), while image focusing is effected by the crystalline lens, a sort of
25 natural lens which, by increasing or decreasing its power, permits a correct vision.

As is known, every alteration of the eye structure implies an entire series of visual defects which are classified by type and do not allow a correct vision.

30 Background Art

To correct these visual defects such as for example those deriving from myopia, hypermetropia or partial or total crystalline lens removal, the use of artificial intraocular lenses, sometimes designated by the acronym "IOL" (Intra Ocular Lens) has become popular in the art. Such lenses, once surgically implanted in the eye of a patient, correct visual defects or replace the crystalline lens depending on the case.

These lenses essentially comprise an optical part generally consisting of a lens portion having a defined power, and a supporting or non-optical part for firmly retaining the lens within the eye and centering the optical part in the pupillary zone.

A first type of intraocular lens as described e.g. in U.S. patents 3,673,616, 3,994,027 and 4,143,427 is implanted in the anterior chamber of the eye, i.e. in the zone between the iris and the cornea.

This kind of intraocular lens, although relatively easy to implant, shows a series of drawbacks essentially related with the irritating action that the support means (loops) of the optical part exert on the sensitive internal eye structures.

Thus, for example, intraocular lenses in which the supporting loops are positioned in the corner between cornea and iris may entail an increase in intraocular pressure and may cause the onset of glaucoma, being the ducts which allow evacuation of aqueous humor from the eye positioned in such corner between cornea and iris.

In addition, the supporting loops located in the corner between cornea and iris could accidentally touch the corneal endothelium and cause endothelial dystrophy with loss of corneal transparency.

Anterior chamber intraocular lenses in which the supporting loops are directly fixed on the iris, on the other hand, require a relatively complex insertion technique which may cause iris irritation (iritis).

- 5 In addition to this, iris-supported lenses may be displaced with all the resulting negative consequences.

 A second type of intraocular lens as described e.g. in U.S. patent 4,504,981 provides to implant the optical part of the lens in the posterior chamber of the eye, i.e.
10 in the zone underlying the iris.

 In this U.S. patent, there are essentially described two embodiments of a posterior chamber intraocular lens depending on the presence or absence of the anterior capsule of the crystalline lens.

- 15 In a first embodiment, the optical part of the lens is rested on the anterior capsule of the crystalline lens, while opposite supporting loops are implanted in the ciliary groove posterior to the iris.

 Although this intraocular lens does not damage the
20 sensitive structures surrounding the iris, it was found that its use may cause a displacement of the optical zone from the pupil which is especially fostered by the great eye diameter.

- The optical part resting on the anterior capsule of
25 the crystalline lens may also cause trauma to the latter with all the negative consequences which derive therefrom.

 In a second embodiment of intraocular lens described in the above mentioned U.S. patent and usable in cases where the crystalline lens is totally removed, the optical
30 part is supported in the posterior chamber of the eye by means of supporting loops crossing the iris and laterally supported on the anterior surface thereof.

Similarly to what has been discussed above with reference to anterior chamber intraocular lenses, however, this embodiment may induce all those alterations connected to a limitation of the physiological movements of the pupil
5 which affect the iris and/or the internal elements related therewith.

Disclosure of Invention

Accordingly, the technical problem underlying the present invention is that of conceiving and making
10 available an intraocular lens which would allow to correct visual defects whether in the presence or in the absence of the natural crystalline lens and which would be free at the same time of the shortcomings mentioned with reference to the prior art.

According to the invention, this problem is solved by an intraocular lens of the type mentioned above which is characterized in that said at least one supporting loop is posteriorly connected to the lens portion at a distance such that, once the lens is implanted, said at least one
15 supporting loop is located in the ciliary groove of the eye and the lens portion is located in the anterior chamber of the eye at a preset distance from the iris.
20

Preferably, the lens portion of the intraocular lens has a diameter of from 4 mm to 8 mm and a thickness varying
25 between the central and peripheral portions as a function of the dioptric power and the execution geometry.

The central part of the lens portion may therefore be biconvex, plano-convex, planoconcave, biconcave, aspherical, bifocal or progressive being the most
30 appropriate thickness readily determinable by one skilled in the art depending on lens type and power.

Preferably, the thickness of the central part of the

lens portion varies from 0.15 to 3 mm, while the thickness of the peripheral portion ranges between 0.30 and 2.50 mm.

According to a preferred embodiment, the intraocular lens of the invention comprises a single supporting loop of the lens portion, having a length of from 10 to 30 mm, values which substantially correspond to 40% and, respectively, to 90% of the circumference of the ciliary groove of the eye.

Preferably, the supporting loop extends along an arc of a circle having a radius of from about 5 to about 7 mm (which correspond to a diameter of from 10 to 14 mm), which corresponds to the average radius of the ciliary groove.

Still more preferably, the supporting loop has a length of from 15 to 25 mm which are values substantially corresponding to about 45% and, respectively, to 75% of the circumference of the ciliary groove of the eye.

Preferably, furthermore, the supporting loop has a thickness of from 0.15 to 1 mm and comprises an enlarged end portion having a substantially spherical shape, which facilitates its implantation through the iris and its positioning in the ciliary groove of the same.

According to the invention, the lens portion and the corresponding supporting loop lie in substantially parallel planes, mutually spaced at a distance slightly greater than the average iris thickness, so as to avoid any contact therewith once the lens is implanted in the eye.

Preferably and taking into account the average physiological values, this distance ranges from 0.8 to 2.5 mm.

Thanks to these structural features, the intraocular lens of the invention advantageously allows to position its optical part (lens portion) in the anterior chamber and its

non-optical part (supporting loop) in a physiologically inert zone of the posterior chamber of the eye, the ciliary groove, thus allowing to correct visual defects both with and without the natural crystalline lens and without
5 injuring in any way the sensitive eye structures.

Preferably, the supporting loop is connected to the lens portion by a junction arm, having an appropriate geometrical shape described in greater detail below, extending between the parallel planes identified
10 respectively by the lens portion and by the supporting loop.

In a first embodiment of the invention, the junction arm radially protrudes from the plate and comprises a first portion, substantially rectilinear and coplanar with the
15 lens portion, and a second portion, substantially shaped as an arc of a circle, extending between the plane of the lens portion and the plane of the supporting loop with which it defines an angle having a value ranging from 15° to 60°.

Advantageously, the second portion of the junction
20 arm is substantially shaped as a semicircle and constitutes respective spring means designed to retain the lens portion and its supporting loop at a preset distance as defined above.

In other words, the second portion of the junction
25 arm constitutes a sort of "spring" capable of facilitating the lens implantation in the eye and holding the lens in place once implanted, counterbalancing any force directed perpendicularly to the plane of the lens portion.

Advantageously, it was observed that optimal
30 elasticity characteristics of the lens are achieved when the radius of curvature of the above mentioned second semicircular portion varies from 0.6 to 3.5 mm, values which correspond to 1/8 and, respectively, to 1/2 of the

minimum and maximum values of the radius of the lens portion supporting loop.

According to a second embodiment of the invention, the junction arm between the lens portion and the
5 respective supporting loop tangentially extends from the lens portion and comprises a first portion, substantially shaped as an arc of a circle and coplanar with the lens portion and a second portion, also substantially shaped as an arc of a circle and extending between the plane of the
10 lens portion and the plane of the supporting loop with which it defines the above mentioned angle having a value of from 15° to 60° .

Preferably, both portions of the junction arm are appropriately shaped by using different curvature radii.

15 More particularly, the first portion of the junction arm has a curvature radius decreasing from a value of about 3 mm down to a value of about 1 mm, while the second portion of the junction arm has a curvature radius increasing from said minimum value up to a value of from 5
20 to 7 mm, essentially equal to the radius of the supporting loop of the lens portion.

Although the arc-shaped structure of the second or of both portions of the junction arm is the most advantageous and allows an easy implantation of the intraocular lens,
25 this portion or arm may have any other geometrical shape, such as for example that of an angle with a beveled edge, suitable for ensuring the desired degree of elasticity (spring effect) in a direction perpendicular to the plane of the lens portion.

30 According to a second embodiment, the intraocular lens of the invention may comprise a pair of supporting loops which are mirror images of each other, extending from diametrically opposite parts of the lens portion.

Preferably, each of said loops possesses structural features essentially identical with those described above with reference to the one-loop embodiment except for the total length, which in this case is more limited and preferably ranges from 7 to 15 mm.

In this embodiment both the supporting loops are preferably connected to the lens portion through a single junction arm tangentially extending from the plate.

To facilitate the implantation operations of the lens in the eye, one of the two loops may be longer than the other, and preferably has a length which is from 1 to 5 mm longer.

Although they may be made in separate parts mutually assembled in a known manner, for example by means of glueing and/or welding, according to a particularly advantageous embodiment of the invention the lens portion, the junction arm and the supporting loops are integrally formed in a single piece of an appropriate biocompatible plastics material.

Preferably, this biocompatible plastics material is selected from the group comprising suitable materials such as, for example, polymethyl methacrylate and its so-called heat-sensitive derivatives, or so-called 'soft' materials such as, for example, silicone polymers and the well-known hydrogels in their various forms.

Examples of hydrogels suitable for the purposes of the invention are hydroxyethyl methacrylate and polyvinyl pyrrolidone.

In another embodiment of the invention, the optical portion of the lens may be made of a so-called 'soft' biocompatible polymeric material and the non-optical part (supporting loop or loops) may be made of a so-called

'hard' material, such as for example methacrylates and their derivatives.

Additional features and advantages of an intraocular lens according to the invention will be more readily
5 apparent from the following description of a preferred embodiment thereof, given by way of non-limiting example with reference to the annexed drawings.

Brief Description of Drawings

In the drawings:

10 - FIG. 1 shows a top plan view of an intraocular lens according to the present invention;

- FIG. 2 shows a side elevational view, in partial cross section taken along line II-II of FIG. 1, of the intraocular lens of said figure;

15 - FIG. 3 shows a top plan view of the intraocular lens of FIG. 1 implanted inside the eye;

- FIG. 4 shows a side elevational view, in partial cross section taken along line IV-IV of FIG. 3, of the intraocular lens of that figure, in which some anatomical
20 details of the eye are illustrated;

- FIG. 5 shows a top plan view of a second embodiment of an intraocular lens according to the present invention;

- FIG. 6 shows a side elevational view, in partial cross section taken along line VI-VI of FIG. 5, of the
25 intraocular lens of said figure.

Modes for Carrying Out the Invention

With reference to the figures, reference number 1 globally indicates an intraocular lens according to the present invention.

The intraocular lens 1 is in the case in question a planoconcave lens and comprises a lens portion 2 having a planar posterior surface 2b and a slightly concave anterior surface 2a.

5 The lens portion 2 is connected to a supporting loop 3 substantially shaped as an arc of a circle having a diameter substantially equal to the diameter of the ciliary groove of the eye 4.

10 The supporting loop 3 is designed to fix the lens in the eye 4 and is posteriorly connected to the lens portion 2 at a distance "d" not lower than the thickness of the iris 5 which preferably ranges from 0.8 to 2.5 mm.

15 In this way, when the lens is implanted the lens portion 2 and the supporting loop 3 are respectively located in the anterior chamber 6, defined between the iris 5 and the cornea 7, and in the ciliary groove 8 defined in the posterior chamber 9 of the eye 4, thus avoiding that the lens portion 2 touches in any way the iris or the crystalline lens 11 (FIG. 4).

20 The supporting loop 3 is connected to the lens portion 2 by means of a junction arm 10, radially extending from the lens portion 2 at a center-line plane A-A thereof, connected to the lens portion 2 by means of a first portion 10a which is substantially rectilinear and coplanar with
25 the same.

30 The junction arm 10 further comprises a second portion 10b, substantially shaped as an arc of a circle, extending as a prolongation of the portion 10a between the plane B-B of the lens portion 2 and the plane C-C of the supporting loop 3 with which the arm second portion defines an angle α having a value of from 15° to 60°.

Advantageously, the portion 10b of the junction arm

is essentially shaped as a semicircle with a limited curvature radius and constitutes respective spring means designed to hold the lens portion 2 and its supporting loop 3 at the preset distance "d" as defined above.

5 The supporting loop 3 is preferably integral with the junction arm 10 and with the lens portion 2 and has a length of from 10 to 30 mm (40%-90% of the ciliary groove 8 circumference of the eye 4).

10 In a particularly advantageous embodiment, the supporting loop has a length ranging from 15 to 25 mm (about 45%-75% of the ciliary groove 8 circumference of the eye 4).

15 Advantageously, furthermore, the supporting loop 3 comprises an enlarged end portion 3a having a substantially spherical shape which facilitates its insertion through the iris 5 and its subsequent positioning in the ciliary groove 8 of the eye 4.

20 According to the invention, the intraocular lens 1 may be manufactured using polymethyl methacrylate or another suitable biocompatible plastics material, by means of known techniques such as, for example, by lathe working and milling, molding or semimolding.

25 Preferably, the intraocular lens 1 is made by lathe working and milling starting from a blank of the selected material and using a four-axis lathe which allows completion of the surfaces in a continuous and progressive manner.

30 According to the invention, the intraocular lens 1 may be implanted in the eye 4 of a patient by means of any surgical technique suitable for the purpose.

The implant technique of preferred use provides to preliminarily carry out a scleral, corneal or corneoscleral

cut and to subsequently insert the supporting loop 3 in the ciliary groove 8 of the eye, considered physiologically inert, after traversing a cut 12 made in the basal coloboma of the iris 5 (FIG. 3).

5 Advantageously, the insertion of the supporting loop 3 is facilitated by the spherical end portion 3a and takes place by imparting a clockwise rotation to the intraocular lens 1.

10 In this way, the supporting loop 3 may be progressively positioned within the ciliary groove 8, reducing down to a minimum the traumas affecting the eye as a whole, until the loop is entirely implanted and the lens portion 2 is positioned in the anterior chamber 6 at the preset distance from the iris 5.

15 Advantageously, after positioning, the lens portion 2 is not in contact neither with the iris 5 nor with the cornea 7 of the eye 4 nor with any other sensitive structure from a physiological viewpoint (FIG. 4).

20 FIGS. 5 and 6 schematically show another embodiment of the intraocular lens of the present invention.

25 In the following description and in said figures, the elements of the lens structurally or functionally equivalent to those illustrated above with reference to FIGS. 1 to 4 are indicated by the same reference numbers and will not be further described.

 In the embodiment illustrated in FIG. 5 there are two supporting loops 14, 15 of the lens portion 2 symmetrically extending in a specular fashion from diametrically opposite parts thereof.

30 Both the supporting loops 14, 15 are substantially shaped as an arc of a circle having a diameter substantially equal to the diameter of the ciliary groove

of the eye 4 and have a different length, which is respectively greater for the loop 14 and smaller for the loop 15.

In the example illustrated, the loop 14 has a total
5 length of 12 mm, while the loop 15 has a total length of 9 mm.

The total length of the two loops 14, 15 is thus 21 mm.

In this second embodiment, the loops 14, 15 are
10 connected to the lens portion 2 by means of respective junction arms 16, 17 tangentially extending from the lens portion 2 from a center-line plane A-A thereof.

The arms 16, 17 are connected to the lens portion 2 by means of a first portion 16a, 17a, substantially arc-
15 shaped and lying in the plane B-B defined by the lens portion 2, which is integrally connected to a second portion 16b, 17b, also substantially arc-shaped, extending as a prolongation of the portion 16a, 17a between the plane B-B and the plane C-C defined by the supporting loops 14
20 and 15.

Similarly to the first embodiment, the portions 16b and 17b of the junction arms 16 and 17 define with the plane C-C an angle α having a value ranging from 15° to 60°.

25 In addition, the portions 16b, 17b of the junction arms 16, 17 advantageously constitute respective spring means for holding the lens portion 2 and its supporting loops 14, 15 at the preset distance "d" defined hereinabove.

30 Similarly to the previous embodiment, both the loops 14, 15 are provided with respective end portions 14a, 15a having a substantially spherical shape which facilitate

their insertion in the ciliary groove 8 of the eye 4.

In this case, the implant technique of preferred use comprises the preliminary realization of a pair of diametrically opposed scleral, corneal or corneoscleral cuts and the subsequent insertion of the supporting loops 14, 15 in the ciliary groove 8 of the eye, which is considered physiologically inert, after traversing a pair of corresponding cuts made in the basal coloboma of the iris 5.

Thanks to the presence of a loop 14 of predominant length, positioning of the intraocular lens 1 is facilitated by the possibility of firstly introducing the spherical ends 14a and then 15a of the loops in the cuts made and then imparting a clockwise rotation to the intraocular lens 1.

Again in this case, the lens portion 2, once implanted, is not in contact neither with the iris 5 nor with the cornea 7 of the eye 4 nor with any other structure sensitive from a physiological viewpoint.

According to the invention, the intraocular lens 1 may be used without distinction in both its embodiments to correct visual defects either in the absence (aphakic eyes) or in the presence (phakic eyes) of the crystalline lens 11, achieving in both cases an advantageous reduction of all those irritating effects caused by the intraocular lenses of the prior art.

Obviously, those skilled in the art may introduce variants and modifications in the above described invention, in order to satisfy specific and contingent requirements, which variants and modifications fall anyhow within the scope of protection as is defined by the appended claims.

CLAIMS

1. Intraocular lens comprising a lens portion (2) connected to at least one supporting loop (3, 14, 15), substantially shaped as an arc of a circle having a diameter substantially equal to the diameter of the ciliary groove (8) of the eye (4) of a patient, for fixing the lens in said eye (4), characterized in that said at least one supporting loop (3, 14, 15) is posteriorly connected to said lens portion (2) at a distance (d) such that, once the lens is implanted, said at least one supporting loop (3, 14, 15) is positioned in the ciliary groove (8) of the eye (4) and said lens portion (2) is positioned in the anterior chamber (6) of said eye (4) at a preset distance from the iris (5).
2. Intraocular lens according to claim 1, characterized in that said at least one supporting loop (3, 14, 15) is posteriorly connected to said lens portion (2) at a distance (d) of from 0.8 to 2.5 mm.
3. Intraocular lens according to claim 1, characterized in that said at least one supporting loop (3, 14, 15) is connected to said lens portion (2) by means of a respective junction arm (10) radially extending from the lens portion (2).
4. Intraocular lens according to claim 3, characterized in that said junction arm (10) comprises a first portion (10a), substantially rectilinear, coplanar with said lens portion (2) and a second portion (10b), substantially arc-shaped, extending between said lens portion (2) and said at least one supporting loop (3, 14, 15) defining therewith an angle (α) of from 15° to 60°.
5. Intraocular lens according to claim 4, characterized in that the second portion (10b) of said junction arm (10) has a curvature radius of from 0.6 to 3.5 mm.

16

6. Intraocular lens according to claim 1, characterized in that said at least one supporting loop (3, 14, 15) is connected to said lens portion (2) by means of a respective junction arm (16, 17) tangentially extending from the lens
5 portion (2).

7. Intraocular lens according to claim 6, characterized in that said junction arm (16, 17) comprises a first portion (16a, 17a), substantially arc-shaped and coplanar with said lens portion (2) and a second portion (16b, 17b),
10 substantially arc-shaped, extending between said lens portion (2) and said at least one supporting loop (14, 15) defining therewith an angle (α) of from 15° to 60°.

8. Intraocular lens according to claim 7, characterized in that said first portion (16a, 17a) of the junction arm (16,
15 17) has a curvature radius decreasing from a value equal to about 3 mm down to a value of about 1 mm.

9. Intraocular lens according to claim 7, characterized in that said second portion (16b, 17b) of the junction arm (16, 17) has a curvature radius increasing from a value of
20 about 1 mm up to a value of from 5 to 7 mm.

10. Intraocular lens according to claim 1, characterized in that it comprises a single supporting loop (3) having a length of from 10 to 30 mm.

11. Intraocular lens according to claim 1, characterized in
25 that it comprises a pair of supporting loops (14, 15), posteriorly connected to said lens portion (2) on diametrically opposite parts thereof and having a length of from 7 to 15 mm.

12. Intraocular lens according to claim 11, characterized
30 in that one of said supporting loops (14, 15) has a predominant length.

13. Intraocular lens according to claim 1, characterized in

that said at least one supporting loop (3, 14, 15) comprises an enlarged end portion (3a, 14a, 15a) substantially spherical in shape.

14. Intraocular lens according to claim 1, characterized in
5 that said lens portion (2) has a diameter of from 4 to 8 mm.

15. Intraocular lens according to anyone of claims 2 to 14, characterized in that said lens portion (2), said junction arm (10, 16, 17) and said at least one supporting loop (3,
10 14, 15) are integrally formed in a single piece of a biocompatible plastics material.

16. Intraocular lens according to claim 15, characterized in that the biocompatible plastics material is selected from the group comprising: polymethyl methacrylate and
15 derivatives thereof, silicone materials and hydrogels.

17. Intraocular lens comprising a lens portion (2) connected to at least one supporting loop (3, 14, 15), substantially shaped as an arc of a circle having a diameter substantially equal to the diameter of the ciliary
20 groove (8) of the eye (4) of a patient, for fixing the lens in said eye (4), characterized in that said at least one supporting loop (3, 14, 15) is posteriorly connected to said lens portion (2) at a distance (d) of from 0.8 mm to 2.5 mm.

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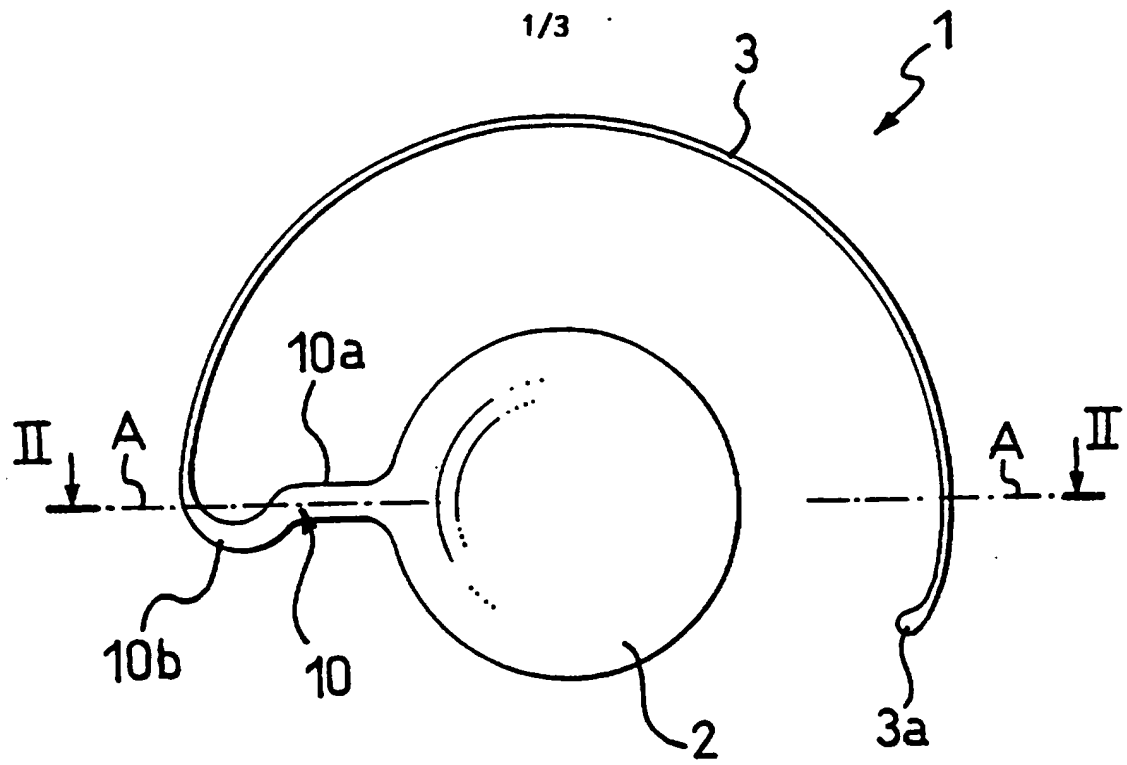


FIG.1

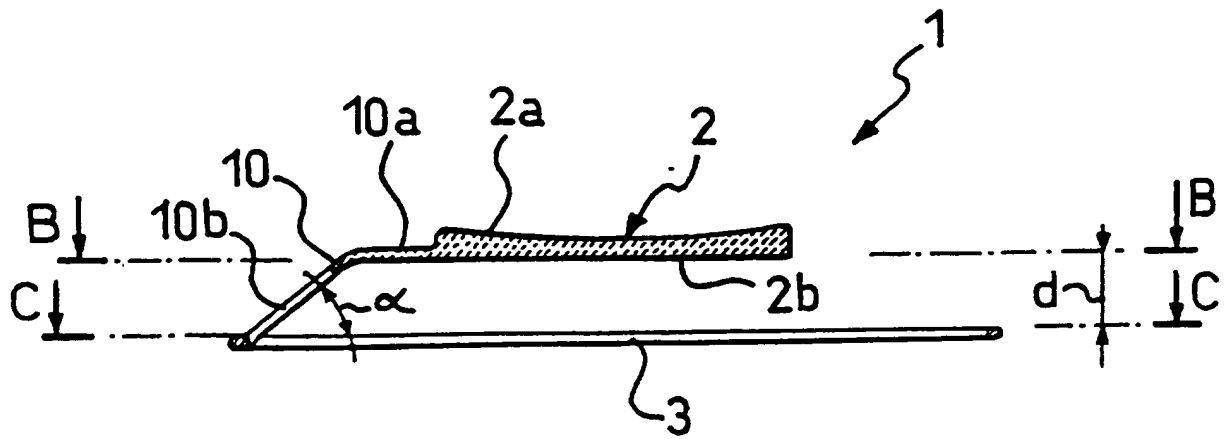


FIG.2

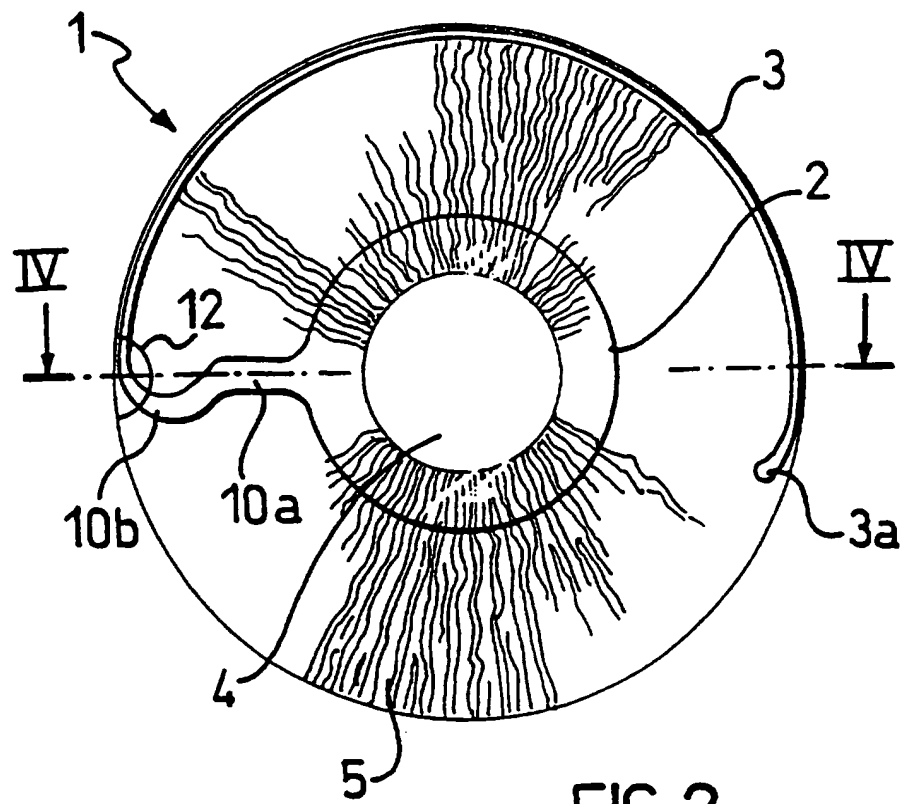


FIG. 3

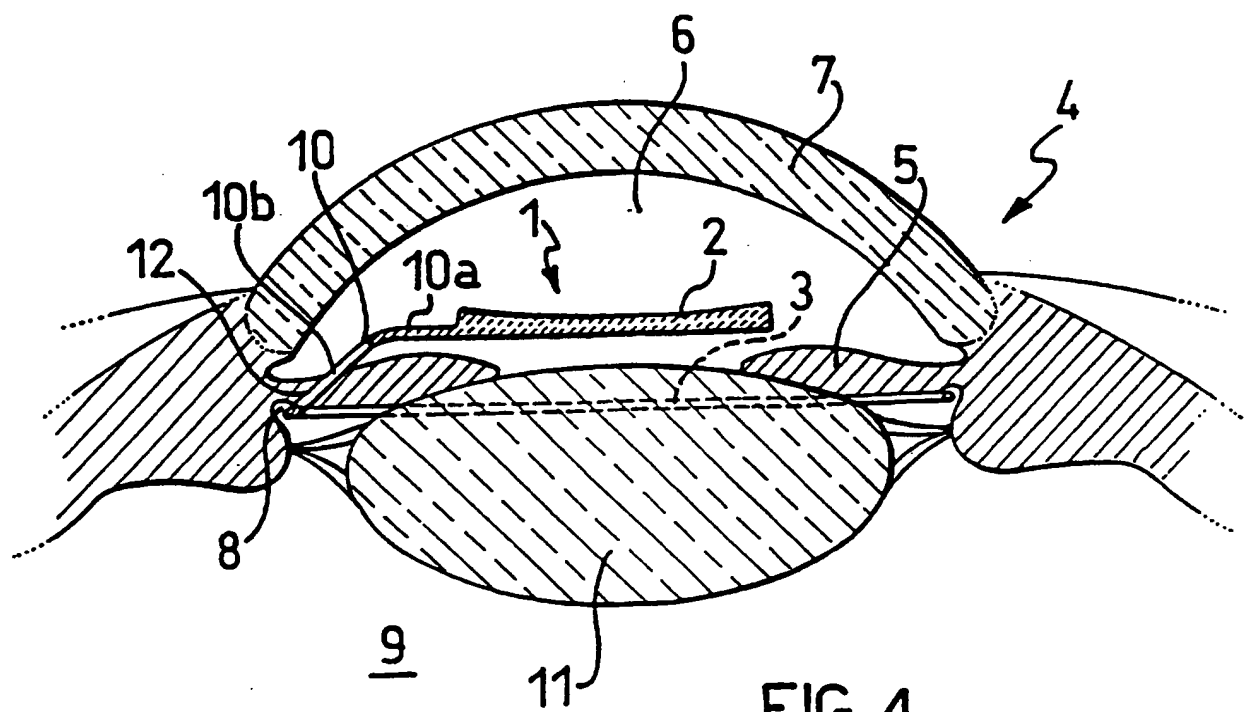


FIG. 4

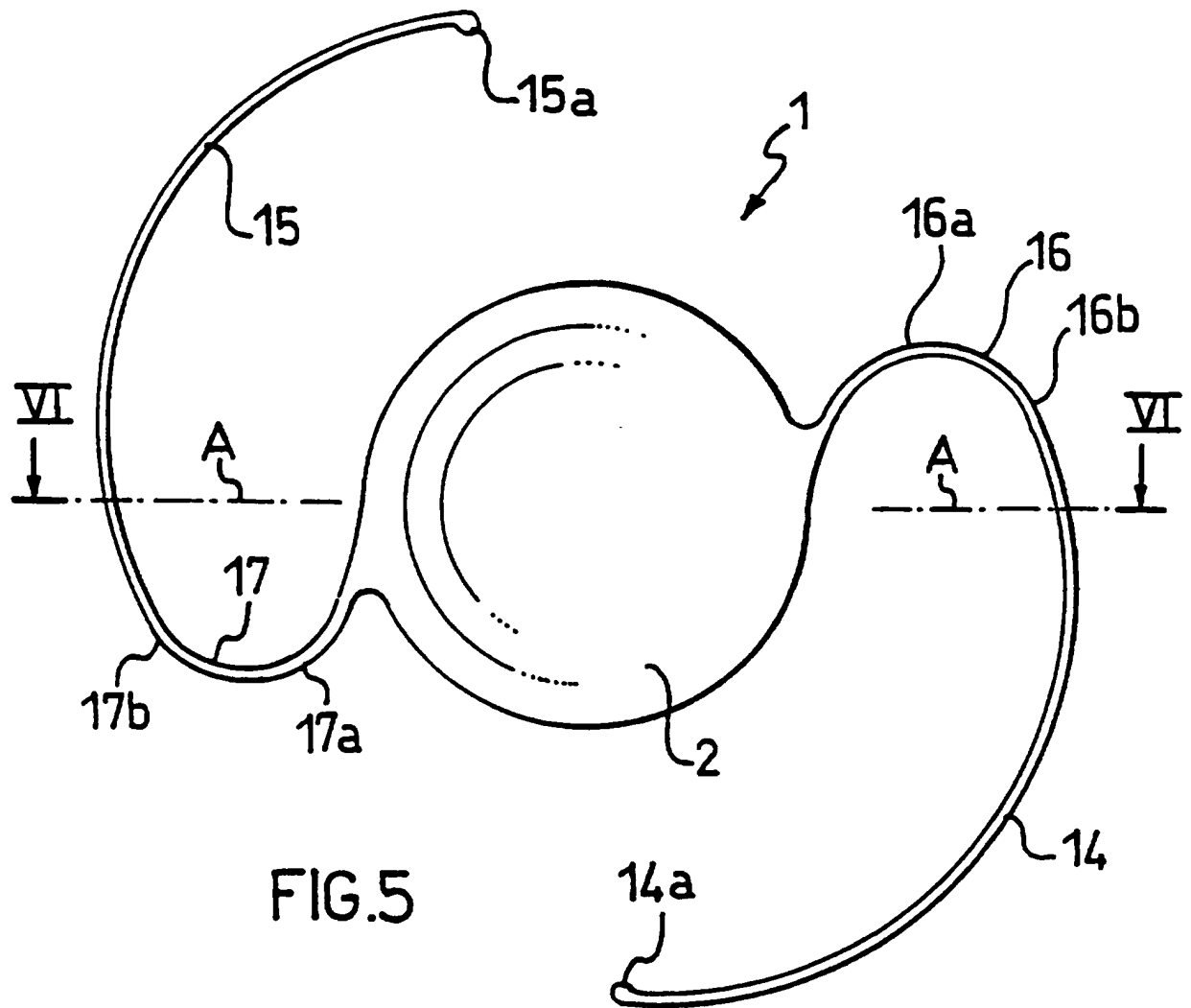


FIG. 5

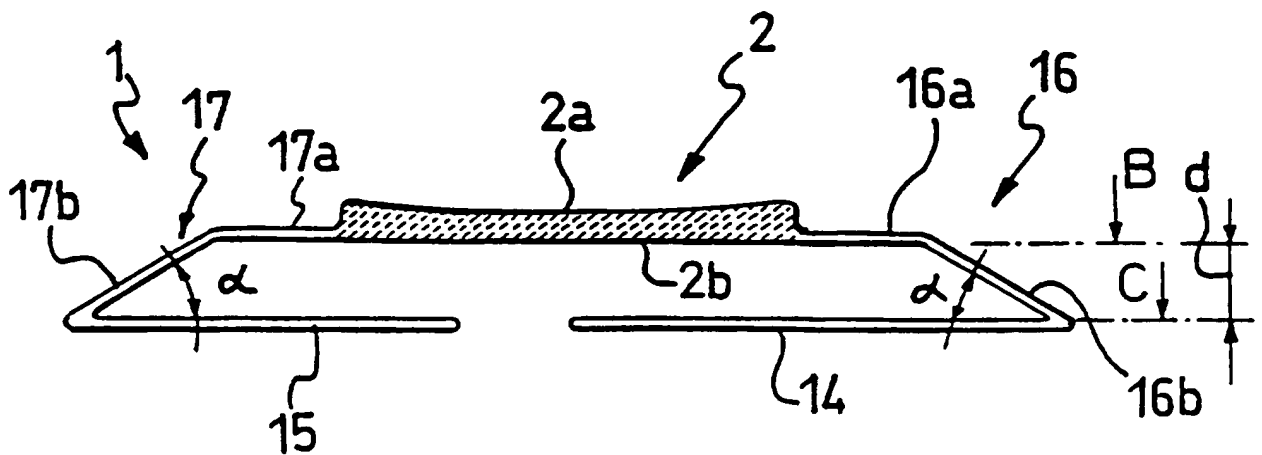


FIG. 6

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61F2/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 346 245 A (LABORATOIRES DOMILENS) 13 December 1989 see column 5, line 28 - line 39; figure 6 see column 4, line 62 - column 5, line 17; figures 4,5 ---	1,2,4,6, 7,11, 14-17
A	EP 0 338 847 A (MANSON) 25 October 1989 see abstract; figures ---	1,10
A	EP 0 069 089 A (MAGGI) 5 January 1983 see abstract ---	1
A	WO 90 07914 A (PHARMACIA) 26 July 1990 see abstract; figures ---	3,11
A	EP 0 061 282 A (KELMAN) 29 September 1982 see abstract; figures ---	12
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

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